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TITLE OF CASE <i>Do not include "a case report"</i>
Acute hyperkalemia in a captive Persian leopard (<i>Panthera pardus saxicolor</i>) immobilized with a ketamine-medetomidine combination.
SUMMARY <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i>
A 12 year old, captive male Persian leopard (<i>Panthera pardus saxicolor</i>) required general anaesthesia for examination and treatment of a recurrent oral fistula. Medetomidine (0.065 mg/kg) and ketamine (3.6 mg/kg) administered intramuscularly by blowpipe darting effectively immobilized the animal that was maintained under general anaesthesia with inhaled isoflurane. In absence of clinical signs, acute hyperkalemia (7.26 mmol/l) was incidentally recognized by the end of anaesthesia. Factors that might have played a role in hyperkalemia development, such as the use of alpha-2 adrenoceptor agonists, stress response, acidosis or dopamine administration are discussed. Hyperkalemia should be considered as a potential complication while anaesthetizing large non-domestic felids.
BACKGROUND <i>Why you think this case is important – why did you write it up?</i>
Large felids require general anaesthesia for medical interventions because of the potential risk of fatally harming the personnel involved. Medetomidine in combination with ketamine has been successfully used to immobilize a large variety of non-domestic mammals,

including large felids, with an apparent wide safety margin.[1]

The Persian leopard (*Panthera pardus saxicolor*), the largest of the leopard subspecies, is considered vulnerable according to the International Union for Conservation of Nature (IUCN).[2] The present report describes a case involving a captive Persian leopard that developed acute hyperkalemia after blowpipe remote immobilization with a ketamine-medetomidine combination and maintenance of anaesthesia with isoflurane. The anaesthetic management of the leopard and possible mechanisms responsible for the increase in serum potassium concentration are presented and discussed.

CASE PRESENTATION *Presenting features, clinical and environmental history*

A 12 year old captive male leopard (*Panthera pardus saxicolor*) required general anaesthesia for examination and treatment of a recurrent oral fistula. The plan was to dart the leopard at the animal park. Thereafter, the animal would be transported under general anaesthesia to the Veterinary Hospital of the University of Bern, where diagnostic tests and adequate treatment would be performed. The main anaesthetic consideration was to assure safety at all stages. Anticipated potential complications were spontaneous arousal, hypoventilation, hypoxemia, hypothermia, hypotension and bradycardia.

The animal was fasted for 24 hours. It was weighed 69.0 kg once anaesthetized. Drugs were initially administered for an estimated weight of 60.0 kg but are presented here based on its real weight. On the day of the procedure, medetomidine 0.058 mg/kg (Zalopine; 10 mg/ml, Orion Pharma, Espoo, Finland) and ketamine 2.9 mg/kg (Ketasol, 100mg/ml, Graueb, Switzerland) were administered intramuscularly (IM) by blowpipe darting at the animal park facilities. For darting, the leopard was restrained in an isolated room, and quietly approached from the other side of the front grid by two veterinarians (SH and SDB). Both veterinarians had blowpipes pointed to the animal, but only one was charged with the drawn-up dart. The other uncharged blowpipe was used to divert the attention of the leopard. The veterinarians were placed on each corner of the front grid, and the leopard positioned itself approximately 4 meters away on the other side of the cage. Once it was distracted and in a good visualization field, a 3 ml air pressurized dart (Mini-Ject 2000 Nylon syringe cylinder; Dist-inject) was shot into the left hindquarter musculature.

Ten minutes after darting the leopard was recumbent but ear twitch reflex was still present, therefore ketamine (0.7 mg/kg) and medetomidine (0.007 mg/kg) (Dorbene; 1 mg/ml, Zoetis) were administered IM by hand into the cervical musculature. Immobilization period was smooth and uneventful. Physical examination was performed after immobilization, HR was 68 bpm, RR 20 and temperature 37.6°C. Five minutes later, the trachea was intubated with a cuffed endotracheal tube (16 mm internal diameter) via the orotracheal route. Thereafter isoflurane (Attane; Provet AG, Lyssach, Switzerland) was administered at 1% in oxygen through a rebreathing system (Matrx VME, Midmark). The animal was then driven to the veterinary university hospital in a secured transport cage in sternal recumbency, under permanent observation of the anaesthetist.

Forty minutes after immobilization the leopard arrived at the hospital facilities. The animal was disconnected from the anaesthesia machine and rapidly moved into the CT room. Once there, the anaesthesia was continued with isoflurane in oxygen and air mixture (50%-50%) (Aespire View, GE Healthcare) and standard monitoring of physiological parameters (ECG, SpO₂, non-invasive arterial blood pressure, spirometry, breathing gas analysis) was instituted. An 18G intravenous catheter was placed in the right cephalic vein and a blood sample was collected immediately after in EDTA and heparin for haematology and biochemistry, respectively. Plasmalyte solution (Plasma-Lyte A, Baxter SA, Volketswil, Switzerland) was administered intravenously (IV) at 10 ml/kg/h throughout the anaesthesia. After termination of CT, the leopard was transferred to the operating theatre for left mandibular canine extraction. Before surgical incision, a caudal inferior alveolar (mandibular) block was performed transcutaneously with ropivacaine 0.15 mg/kg (Ropivacain 5 mg/ml, Frasenius AG, Switzerland), and meloxicam 0.2 mg/kg (Metacam 5mg/ml, Boehringer Ingelheim, Basel, Switzerland) was administered IV. During the surgery, the leopard maintained spontaneous breathing at 15 breaths/min, 1 L tidal volume, SpO₂ was 98 per cent and P_ECO₂ was 36-43 mmHg. Fifteen minutes after surgery started (120 minutes after immobilization, 80 minutes after initiating monitoring), the arterial blood pressure (measured by automated oscillometry with the cuff placed over the left radial artery) decreased from 125/75/50 mmHg to 100/60/40 mmHg (systolic/mean/diastolic SAP/MAP/DAP, respectively) as confirmed by repeated measurements. The expired isoflurane concentration was judged adequate and a dopamine infusion was started at 7 µg/kg/min. Ten minutes later, HR decreased from 65 to 55 bpm and MAP was maintained at 70 mmHg. No arrhythmia was recognized on the ECG. The surgical intervention lasted for 45 minutes and a final blood sample (in EDTA and heparin) was then collected from the left jugular vein (150 minutes after immobilization). Isoflurane was discontinued, all the instrumentation was removed and the leopard was placed on sternal position in the transport secured cage. Once inside, atipamezole 0.33 mg/kg (Antisedan, 5 mg/ml, Orion Pharma) was administered IM and the leopard was extubated afterwards. At this time point, HR was 65 bpm, RR 18 and temperature 35.9 °C. At this stage, no complication had been noticed.

INVESTIGATIONS *If relevant*

Bloodwork was performed twice. First sample was taken 60 minutes after immobilization and all measured haematology and biochemistry values were considered unremarkable based on literature. Potassium serum concentration was 4.4 mmol/L. In contrast (incidental finding), the second bloodwork taken 150 minutes after immobilization revealed biochemical and electrolyte disturbances: Elevated plasma potassium (7.26 mmol/L), creatinine (191 µmol/L) and glycemia (23.55 mmol/L); reduced natremia (139 mmol/L) and chloremia (102 mmol/L).

DIFFERENTIAL DIAGNOSIS *If relevant***HYPERKALEMIA**

- Drug induced hyperkalemia.
- Stress response leading to hyperglycemia.
- Acidosis.
- Decreased urinary potassium excretion.
- Excessive potassium supplementation.
- Pseudohyperkalemia.
- Renal insufficiency.
- Acute cell-tissue breakdown.

TREATMENT <i>If relevant</i>
No treatment was initiated because the results were received after recovery from anaesthesia.
OUTCOME AND FOLLOW-UP
Twenty minutes after atipamezole administration, the leopard recovered uneventfully. Once the animal was bright, responsive and alert, it was transported back to the animal park facilities without incident.
DISCUSSION <i>Include a very brief review of similar published cases</i>
<p>Medetomidine (0.065 mg/kg) and ketamine (3.6 mg/kg) administered intramuscularly by blowpipe darting effectively immobilized this captive Persian leopard (<i>Panthera Pardus saxicolor</i>) that was maintained under general anaesthesia with inhaled isoflurane. However, acute hyperkalemia developed during anaesthesia.</p> <p>The selection of the drug protocol used was based on review of the published literature and experience from colleagues. Chemical immobilization of leopards (<i>Panthera pardus</i>) has been previously described using xylazine and ketamine at a dose of 1.4-1.5 mg/kg and 5 mg/kg respectively.[3,4] Effective combinations of ketamine and medetomidine have been reported in other non-domestic felid species including snow leopards (<i>Panthera uncia</i>, 2.5-3.0 mg/kg ketamine and 0.06-0.08 mg/kg medetomidine),[5] Sunda clouded leopards (<i>Neofelis diardi</i>, 3-4.39 mg/kg ketamine and 0.039-0.054 mg/kg medetomidine),[6] jaguars (<i>Panthera onca</i>, 4.4 mg/kg ketamine and 0.04 mg/kg medetomidine),[1] and lions (<i>Panthera leo</i>, 1.0-5.7 mg/kg ketamine and 0.048-0.058 mg/kg medetomidine).[7] The present leopard had also been effectively anaesthetized previously with this combination.</p> <p>Acute peri-anaesthetic hyperkalemia has been reported in non-domestic large felids including lions, tigers, cheetahs, cougars and jaguars, but not yet in leopards.[8–11] In all the former reports, alpha-2 adrenoceptor agonists and ketamine have been used to immobilize the felids and isoflurane for anaesthesia maintenance. A progressive increase in plasma potassium and glucose concentrations with a decrease in plasma insulin concentration was observed in 8 tigers and 3 lions.[9] Hyperkalemia (6.5 mEq/l) was reached in one tiger only 150 minutes after induction of anaesthesia. Common features between these cases including the leopard presented here are the drugs used (alpha-2, ketamine, isoflurane) in large felids and the slow development of hyperkalemia. It was hypothesized that the increase in plasma potassium concentration occurred as a result of a decrease in plasma insulin concentration caused by medetomidine.[9] However, the causes and mechanisms are still unclear.</p> <p>Hyperkalemia is a potentially life-threatening condition. Main clinical consequences are muscle weakness, and severe cardiac rhythm abnormalities secondary to prolonged depolarization and repolarization of the myocardial conduction. However, clinical suspicion often arises while high potassium concentrations have already been reached. The severity of the manifestations depends not only on the potassium serum concentrations but also on the speed of onset of hyperkalemia.[12] Identification of patients at risk is essential to suggest routine peri-</p>

anaesthetic monitoring of electrolytes and allow for early recognition of the condition. This appears to be necessary in large felids requiring chemical immobilization.

Hyperkalemia can result from increased intake or supplementation, translocation from the intracellular to the extracellular space, decreased renal excretion, or pseudohyperkalemia.[13] In the present case, pseudohyperkalemia was not considered because the haematologic values were unremarkable for both blood samples. Moreover, excessive intake was also unlikely because potassium was solely supplemented through balanced fluid therapy with physiologic concentration of potassium (Plasmalyte-A, 5 mEq/l of potassium) at a rate of 10 ml/kg/h. More probably, translocation of potassium from the intracellular to extracellular space and a reduced urinary excretion both contributed to the development of hyperkalemia in the present case.

Stress response is a complex neuroendocrine response that implies important metabolic changes through the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, leading to increased catecholamines and cortisol, reduced insulin and hyperglycemia among others.[14] Hyperglycemia occurs in proportion to the intensity of the stressor as a result of low insulin concentration, high glucagon concentration and the anti-insulin effects of catecholamines and cortisol.[14] Stress response can be triggered by physical and psychological stressors like fasting, capture anxiety or nociceptive stimulation. There are evidences that stress response is elicited under anaesthetic conditions in humans as well as in animal species.[15–18] Plasma concentrations of cortisol, noradrenaline and insulin may inform on the amplitude of this stress response, but were not analyzed in the present case. Although the approach was planned in order to reduce stress and anxiety, the stressors of capturing a wild animal are not avoidable. Stress response may have contributed to the increase in plasma glucose leading to hyperkalemia in the leopard.

Medetomidine is an alpha-2 adrenoceptor agonist, and has been reported to attenuate the stress response directly through sympatholytic activity, as well as indirectly through sedative and antinociceptive activity.[18–21] Nevertheless, medetomidine may have contributed to development of hyperkalemia. Agonists of the alpha-2 adrenergic receptor (α_2 -AR) inhibit insulin secretion from pancreatic β cells (α_{2A} -AR subtype),[22] which results in hyperglycemia. Medetomidine has been reported to cause hyperglycemia in rats, cattle, dogs and cats;[23–27] among them the greatest elevation in plasma glucose was found in cats.[28] Both insulin deficiency (leading to a decreased cellular uptake of potassium) and hyperglycemia (leading to hyperosmolality and cellular water loss) can lead to hyperkalemia.[12] This is in agreement with observations from Reilly et al. in lions and tigers.[9] Still, it appears unclear why hyperkalemia develops hours later after medetomidine administration.

Other drugs have been reported for chemical immobilization of large felids and may help to limit occurrence of hyperkalemia. Tiletamine-zolazepam combination has been reported in cheetahs and small non-domestic felids immobilization.[29,30] The use of potent opioids as etorphine or carfentanil has also been reported to immobilize other non-domestic mammals,[31,32] however neither its effectiveness or safety is documented in non-domestic felids. According to the literature, despite the risk for hyperkalemia, combinations of an alpha-2 adrenoceptor agonist and ketamine remain the most recommended choice of drugs. Further

investigations would be required to find an alternative drug for immobilizing these species.

Acidosis is another potential cause of hyperkalemia. With lowering pH, potassium is shifted from the intracellular space into the extracellular in exchange for hydrogen ions.[13] In the present case, no blood gas analysis was run and occurrence of acidemia cannot be excluded. The $P_{\text{E}}\text{CO}_2$ was maintained between 36 to 43 mmHg under spontaneous ventilation throughout the anaesthesia such that respiratory acidosis is unlikely, but metabolic acidosis was not tested.

Impaired urinary excretion can also lead to hyperkalemia. Urinary potassium excretion is mediated by aldosterone hormone, which increases sodium reabsorption and potassium secretion in the distal nephron.[12] In case of hyperkalemia, aldosterone secretion is stimulated in order to facilitate excretion and normalize blood potassium concentration. In addition, stress response can also promote aldosterone secretion through ACTH. However, in this case dopamine administration may have impaired excretion as shown in vivo in human beings.[33,34] Dopamine inhibits aldosterone production via D2 receptors in the adrenal cortex affecting the late phase of aldosterone biosynthesis as shown in vitro.[35] How quick this mechanism can lead to significant hyperkalemia is unknown and other cases of hyperkalemia were not associated with dopamine. It remains unclear if the administration of dopamine for approximately 30 minutes may have partially contributed to the development of hyperkalemia. Epinephrine, norepinephrine or dobutamine are alternative to dopamine for cardiovascular support and may limit impairment of potassium excretion,[36] but they might affect serum potassium levels through their adrenergic activity.[37]

In the present case, no specific treatment was administered for managing hyperkalemia because biochemistry results were received after recovery and no clinical signs developed. Due to the possible contribution of alpha-2 adrenoceptor agonists to the development of hyperkalemia in non-domestic felids, atipamezole administration might be an effective treatment. Nevertheless, caution should be taken if administered during anaesthesia as arousal and consequent risk for the personnel might occur. Other therapeutic options include drugs that promote potassium shift into the intracellular space, like insulin, dextrose and bicarbonate. Measuring blood pH is indicated to treat acidemia and adjust bicarbonate administration. Fluid therapy will help to restore electrolyte imbalance and support kidney function. It appears sensible to ensure availability of these treatment options when anaesthetizing non-domestic felids, together with ECG monitoring.

In conclusion, a combination of ketamine (3.6 mg/kg) and medetomidine (0.065 mg/kg) was effective to immobilize a captive Persian leopard, however hyperkalemia developed during the anaesthesia. This report, together with previous reports in other large felids species, suggests that hyperkalemia is an important consideration while anaesthetizing these species and must be monitored. Further research is needed to confirm the causing mechanisms and find alternative drug protocols for preventing hyperkalemia.

LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required field

- Hyperkalemia is an important consideration while anaesthetizing large felids.
- Stress response and alpha-2 adrenoceptor agonists might have influence on its development.
- Serial monitoring of electrolytes is recommended, as clinical signs may be not recognizable.
- Hyperkalemia treatment options should be available when anaesthetizing non-domestic felids.
- ~~An alternative to dopamine might be considered if cardiovascular support is needed.~~

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